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# Worms: Pernicious parasites or allies against allergies?

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**Summary**

Type 2 immune responses are most commonly associated with allergy and helminth parasite infections. Since the discovery of Th1 and Th2 immune responses more than 30 years ago, models of both allergic disease and helminth infections have been useful in characterizing the development, effector mechanisms and pathological consequences of type 2 immune responses. The observation that some helminth infections negatively correlate with allergic and inflammatory disease led to a large field of research into parasite immunomodulation. However, it is worth noting that helminth parasites are not always benign infections, and that helminth immunomodulation can have stimulatory as well as suppressive effects on allergic responses. In this review, we will discuss how parasitic infections change host responses, the consequences for bystander immunity and how this interaction influences clinical symptoms of allergy.

## 1 | KEY ELEMENTS IN TYPE 2 IMMUNE RESPONSES

Both allergic disease and helminth infection are associated with type 2 immune responses. Type 2 immune responses are generally required for control of parasite infections and have the advantage of causing reduced collateral damage compared with Th1 or Th17 immune responses. Conversely, in allergy, type 2 responses cause pathology which can be debilitating or even fatal. Models using mice deficient in key elements of type 2 immune pathways have shown the critical role of these responses in parasite killing/ejection, healing, metabolic changes and in allergic pathology.

Type 2 immunity is characterized by the development of antigen-specific IgE immunoglobulins and Th2 cells producing IL-4, IL-5 and IL-13. Upon recognition of antigen, Th2 cell cytokine production leads to the activation of eosinophils, while cross-linking of IgE on primed mast cells leads to their degranulation. Together these effector immune cells are responsible for the clinical symptoms of allergic diseases such as atopic dermatitis, asthma and food allergy.

Interestingly, in both chronically helminth-infected people and individuals who have experienced repeated clinical or environmental exposure to allergen,[1] high antigen-specific IgG4 levels can be found, as well as increased circulating levels of regulatory T cells (Treg) and regulatory B cells (Breg), producing IL-10 and TGF-β.[2,3] Thus, the type 2 adaptive immune response is capable of being tolerized, either through exogenous factors acting on adaptive immune cells, intrinsic exhaustion of those cells or changes in the innate immune system which is required for their activation.

Dendritic cells (DCs) are an innate immune population absolutely required for the development of optimal effector Th cell immune responses, including Th2 responses.[4,5] DCs are intimately associated with barrier sites such as the lungs and will take up antigens from within and beyond the epithelial barrier. Upon detection of a helminth infection or an environmental allergen,[6] DCs become activated and migrate to the draining lymph nodes, presenting antigens to T cells and potentially inducing a Th2 immune response. Although the critical involvement of DCs in Th2 development is

clear, the precise signals that lead to priming of a Th2-inducing DC are incompletely characterized. In recent years, the importance of epithelial-derived cytokines such as interleukin-25 (IL-25), IL-33 and thymic stromal lymphopoietin (TSLP) in allergy and parasitic infection has become appreciated.[7] These cytokines can act directly on DCs, skewing resultant responses to Th2, and also directly activate type 2 innate lymphoid cells (ILC2s), inducing a rapid innate type 2 response.

ILC2s are innate lymphocytes, lacking antigen-specific receptors, which produce large amounts of type 2 cytokines IL-5, IL-13 and IL-9, as well as proresolving factors amphiregulin[8] and IL-10.[9] Activated ILC2s also express class II MHC, can present peptide antigen and can supply IL-4R signals in type 2 response initiation.[10]

Thus, type 2 innate epithelial cell cytokines, DC and ILC2s are involved in the earliest responses to allergens and helminth parasites, in initiation of the Th2 immune response, and in amplification of allergic and antiparasite immunity. However, antigen specificity and the control of ongoing immune responses are critically dependent on adaptive immunity.

## 2 | HELMINTH INFECTIONS, DAMAGE AND TYPE 2 IMMUNE RESPONSES

While type 2 immune responses have clear pathological roles in allergy, they are generally beneficial in helminth infections. Increased susceptibility to a range of intestinal and tissue-dwelling parasites can be seen in mice lacking essential elements of the type 2 response pathway.[11] Likewise, in human populations, single nucleotide polymorphisms (SNPs) in type 2 response elements such as IL-13 and STAT-6, and immunoregulatory elements IL-10 and TGF-β correlate with both decreased susceptibility to allergy and increased susceptibility to parasitic infection.[12-14]

Many helminth species remain in the host for a prolonged time, and type 2 responses may be more beneficial for the survival and integrity of the host than the more inflammatory Th1/Th17 alternative. Indeed, asymptomatic infections with, for example filarial worms are associated with type 2 responses,[15] whereas in individuals suffering from helminth infections linked to pathology and clinical symptoms, Th1 or Th17 cell responses are often found.[16-18] In many parasitic infections, sterile immunity is not common: most individuals living in endemic areas are constantly reinfected, even after drug-mediated clearance of parasites.[19] As a consequence, host immune responses in endemic areas are often characterized as a "modified Th2" response that results in control (but not clearance) of parasite load, low-level parasite transmission and minimal host pathology: an acceptable host/parasite compromise.

Tissue damage caused by helminth infections is also a powerful stimulus for type 2 responses, which in turn lead to a rapid type 2 response-mediated healing phenotype.[20] For example, in the lung, type 2 immune responses are important in healing damage caused by migrating *Nippostrongylus brasiliensis* larvae, while recruiting eosinophils that damage larvae, hamper their fecundity and fertility upon arrival in the gut, leading to an early expulsion.[11] However, type 2 responses may also cause pathology due to aberrant healing, such as in the case of fibrotic granulomas formed around schistosome eggs. These granulomas cause mild to more severe pathology, linked to local fibrotic tissue, liver and splenomegaly, and an increased risk to develop cancer in the liver or the bladder, depending on the species.[21] Thus, depending on context and infecting species, parasite products can induce epithelial cell proliferation, encourage healing, control fibrosis[22] and cause transformation and cancerous growth.[23]

In the absence of helminth infection, type 2 responses are often perceived to be only involved in pathological allergic responses, ultimately leading to decreased lung function and airway hyperactivity in asthma and rhinitis,[24] pruritus (itching) and damage to the skin barrier in atopic dermatitis,[25] and itching, pain and/or swelling of the mouth, pharynx and oesophagus, diarrhoea and abdominal pain in food allergy.[26] However, type 2 responses in the absence of helminth infections can also have beneficial roles: circulating IgE specific to venom toxins, which can cause dangerous anaphylaxis on exposure, can also be protective with release of mast cell proteases that degrade venom toxins and counteract the venom's detrimental effects.[27] During pregnancy, the type 2 cytokine milieu in the womb protects the "non-self" foetus from abortion (which conversely is linked to increased Th1/17 responses).[28] Finally, perinatal type 2 responses in the lung are required for establishment of lung homoeostasis and development of anti-inflammatory type 2 macrophages.[29] Therefore, just as there is no such thing as "weeds" in a garden (just plants in the wrong place) perhaps there is no such thing as a "bad" immune response, just inappropriate in its context. How parasites modulate these useful and/or pathological responses, and what happens when the balance is perturbed, will be covered in the next sections.

## 3 | TALES OF WORMS IN MEN

In the 1970s, the "hygiene hypothesis" was proposed as an explanation for the steep and alarming rise in the prevalence of childhood allergies and asthma among urban, Westernized societies. The hygiene hypothesis links changes in housing, sanitation and health care to increased allergic disease and proposes that this is in part due to reduced endemic infections. The prevalence of parasitic infections in particular has been drastically reduced in Westernized societies over the last century and is therefore proposed to be an important contributing factor in this hypothesis. Multiple epidemiological studies have been used to support this hypothesis by indicating that in helminth-endemic rural areas relatively few people have allergic symptoms.[30,31] The fact that some local African languages contain no words to describe allergic symptoms could support this hypothesis, indicating that allergic diseases have never been a problem among these populations.[32]

However, an examination of the many population studies of the past 30 years either by meta-analyses[33,34] or in some excellent

systematic reviews[35,36] shows that the direction of the effect by helminth infections is far from consistent. For example, while hookworm infections were associated with a protective effect against asthma, other helminths like *Trichuris trichiura*, *Enterobius vermicularis* and *Strongyloides stercoralis* did not show any effect, and conversely *Ascaris lumbricoides* infection increased the risk of developing asthma and wheeze.[33] Greater consensus was observed regarding protection to atopic sensitization and allergic skin reactivity, although the outcome varied with the allergen studied.[34-36]

Similarly, studies using anthelmintic treatment of helminth-endemic populations show mixed results (for a full overview, see Wammes, 2014[35])—some show an increased frequency of allergen skin prick test (SPT) after worm clearance,[37] while others did not observe any differences between treatment and control groups within one or 2 year time frames.[38] Part of the inconsistent findings and dissimilarities in conclusion in the epidemiological and interventional studies may be explained by variations in factors such as the age of the population studied, age of helminth exposure (and consequent early-life immune imprinting) and the infectious burden, endemic parasite species and chronicity of infection, or differences in study parameters such as clinical symptoms in asthma, rhinitis or eczema or methods used to measure allergen sensitization (SPT versus allergen-specific IgE).[35,39] Epidemiological studies applying antihelminthic treatment during pregnancy provide an interesting approach to evaluate the relationship between helminths, early immune priming and allergy: these show an increased risk of early-life eczema in babies of treated mothers[37,40]; however, a 9-year follow-up showed that this effect was not maintained to later life.[41]

In contrast to human studies, experiments in mice showed more consistent findings in the prevention of allergic airway inflammation by a wide range of helminth species: *N. brasiliensis*,[42] *Heligmosomoides polygyrus*,[43] *Litomosoides sigmodontis*,[44] *Schistosoma mansoni*,[45] *Trichinella spiralis*[46] and *Schistosoma japonicum*.[47,48] Interestingly, transmaternal protection against allergic airway inflammation by helminth infection in mice implied that this was dependent on the phase of the infection during pregnancy: offspring from schistosome-infected females were protected if they had mated during the initial Th1 phase, or the chronic immunoregulatory phases of schistosome infection, but conversely disease was exacerbated if mating occurred during the high Th2 phase of infection (coinciding with egg deposition).[49] This may further complicate assessment of human population studies, as protection against allergy may depend on far more complicated interactions than simple presence of infection, but also prenatal stimuli and phase of infection.

## 4 | HELMINTH INTERACTIONS WITH OTHER INFECTIONS AND THE MICROBIOTA

Severe respiratory syncytial virus (RSV) and/or rhinovirus (RV) infection in early life gives a sevenfold increased risk of developing asthma,[50] while asthma exacerbations are associated with concurrent respiratory viral infection in up to 80% of cases.[51] Furthermore, in experimental RV infections of asthmatic volunteers, IL-33 and other type 2 cytokines were released into the airways, correlating with severity of asthma exacerbation.[52] Parasite products can suppress IL-33 release[53,54]; thus, they could directly suppress viral proallergic responses, or, via suppression of IL-33 release, lead to increased antiviral immune responses.[55] Interestingly, the interactions between helminths and viruses have recently received a great deal of attention. For example, *H. polygyrus* infection leads to upregulation of type 1 interferons in the gut and lung, and suppression of respiratory syncytial virus (RSV) titre, with reduced inflammation and lung pathology in a mouse model.[56] Likewise, *S. mansoni* infection suppresses lung pathology during pneumonia virus of mice (PVM) or influenza infection and reduced viral titre.[57] These murine studies suggest that helminth parasites could suppress titre and/or inflammation in viral lung infections with a subsequent effect of reducing the risk of viral-induced development or exacerbation of asthma. Though it is yet unclear whether similar effects can be found in humans, several recent virus-helminth coinfection studies have also reported worsening of viral infection through helminth-mediated immunosuppression; for example, *H. polygyrus* or *S. mansoni* resulted in murine γ-herpesvirus reactivation,[58] while *T. spiralis* infection resulted in impaired immunity to murine norovirus.[59] Notably, in both cases, suppression of antiviral immunity was dependent on STAT-6 and type 2 immune responses. Therefore, suppression of viral responses by helminth parasites depends on viral species and outcomes are dependent on immune mechanisms which control viral proliferation and pathology.

Helminths not only change the response to other infectious agents within the host but can also affect the balance of commensal organisms with which they share an environment. The host genome and the total diversity of the microbiota (the "microbiome") are important in mediating or reflecting health and disease in the intestine, and in other barrier sites such as the lung and skin. Changes in the gut and lung microbiomes are seen in allergic diseases such as asthma,[60] reflecting the immune axis between these mucosal sites or transfer of bacterial populations through processes such as inhalation of airborne bacteria, bacterial migration along mucosal surfaces and microaspiration of gastric contents.[61]

Although many studies of the microbiome focus on faecal contents, it is important to note that intestinal helminths infect specific niches within the intestine: that is *Trichuris* spp in the large intestines, and human hookworms, *H. polygyrus* and *N. brasiliensis* in the small intestines. In humans living in helminth-endemic areas and during experimental helminth infection, helminth infection is associated with increased diversity and abundance of the microbiome.[62-65] Although it has not been demonstrated whether these differences are related to differences in lifestyle and hygiene or causally linked to current helminth infection, the fact that changes in the microbiota are partially abrogated on anthelmintic treatment supports the latter hypothesis.[63] In several

mouse models, intestinal helminth infections induced a decreased prevalence of commensals associated with inflammation[66,67] and increase in commensals associated with immune regulation.[63,68] This is proposed to be an active process, mediated by secreted antimicrobials from the parasite (such as host defence peptides),[69] or mediated by (type 2) immune responses directed against or modulated by the parasite.[63,70] Consequently, changes in the microbiota (due to, eg changes in diet) and microbial metabolite levels (such as short-chain fatty acids) mediate changes in allergic responsiveness.[71] Interestingly, a recent study also found altered fatty acid production by the microbiota of *H. polygyrus*-infected mice and their additional role in protection against allergic airway inflammation.[72]

## 5 | REWORMING THE WEST

The growing support for the idea that helminth infections suppress inflammatory responses led to the proposal of using helminth infections as therapeutic agents in these diseases. In the first clinical trials of "helminth therapy," patients with inflammatory bowel disease (Crohn's disease or ulcerative colitis) were treated with eggs (ova) from the porcine intestinal parasite *Trichuris suis* (TSO), leading to significant reduction in symptom scores in a series of small trials.[73-75] Likewise, an observational study in Argentina showing that multiple sclerosis (MS) patients went into remission after infection with environmentally acquired helminths,[76,77] and when treated to clear their helminth infections, their autoimmune disease was again reactivated.[78] Finally, a series of studies have used human hookworm (*Necator americanus*) in patients with coeliac disease: although initial studies showed no clinically significant difference in responses to gluten challenge,[79] inflammatory immune responses in the gut were reduced and skewed towards a Th2 response.[80,81] In a follow-up open-label study using escalating doses of gluten after hookworm infection, no deterioration in clinical pathology was seen in hookworm-infected subjects[82] giving grounds for further studies.

These initial studies formed the basis of clinical trials treating patients with IBD or multiple sclerosis in the United States and Europe with TSO. However, to date, these trials have shown disappointing

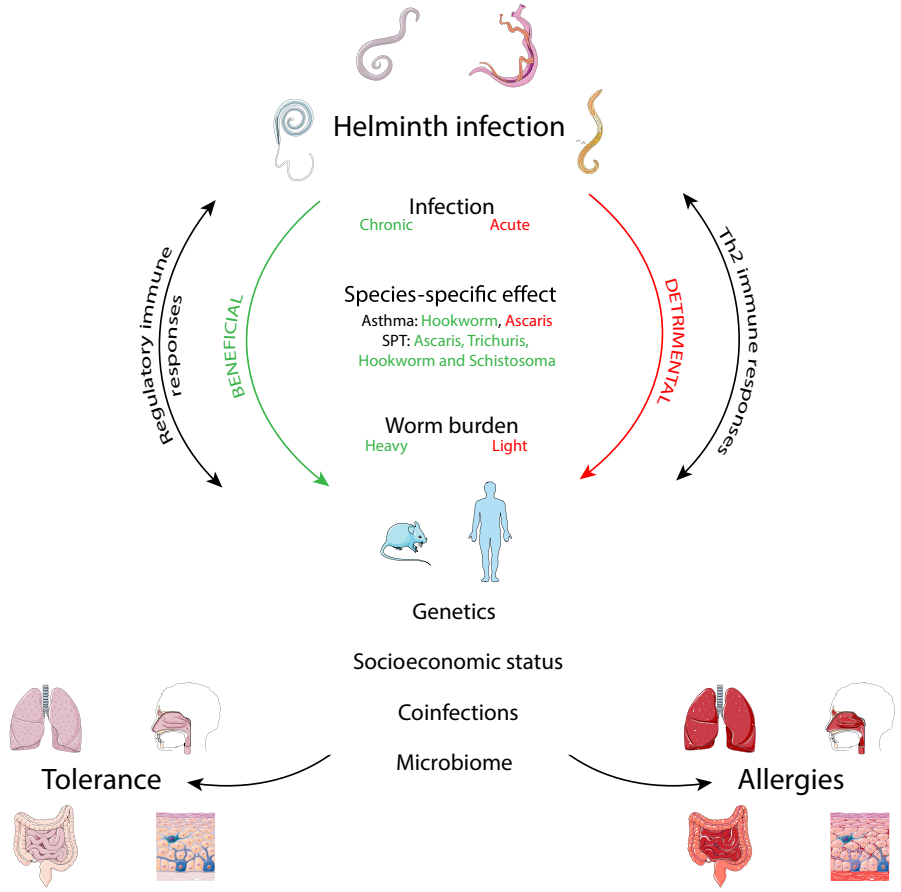


**FIGURE 1** Helminth infections are associated with both promoting and reducing allergic symptoms. Helminths interact strongly with the host immune system, but the type of response is heavily influenced by the chronicity of infection, the species involved and/or worm burden, ultimately tipping the balance towards more detrimental and type 2 response or beneficial and regulatory responses. Subsequently, this balance is further influenced by cofactors such as host genetics, socioeconomic status, coinfections and the composition and diversity of the microbiome leading to the development of clinical symptoms and allergies or tolerance in the host. Image is adapted from Servier Medical ART

response rates and no significant reduction compared with placebo controls.[83-85]

Of most relevance to this review, studies using hookworm infection to treat asthma or TSO to treat allergic rhinitis patients have also been undertaken. However, no change in clinical measurements was seen in either study,[86] and although type 2 specific responses were detected against the hookworm, no regulatory immune responses were found.[87]

Thereby, the promise of helminth therapy has so far not translated to a practicable treatment for human disease. Reasons for this may well include difference between prevention and cure (ie parasitic infection may need to precede allergic sensitization, and effect could be in utero[49]), the difference between infection and administration of parasite products (most of the therapeutic effects in mouse models were based on the application of helminth products rather than a full infection), the single parasite infective dose given (which is generally determined by that which causes no notable side effects, but may therefore be too low and too little for functional suppression of pathology) or disease endotypes which are responsive or refractory to these treatments, precluding statistical significance of effects when the disease population is taken as a whole.[88] Critically, however, the mechanism of action of helminth immunomodulation is not well understood, and whether this is shared between all helminth infections, or more likely unique to each parasitic species, is presently unknown (Figure 1).

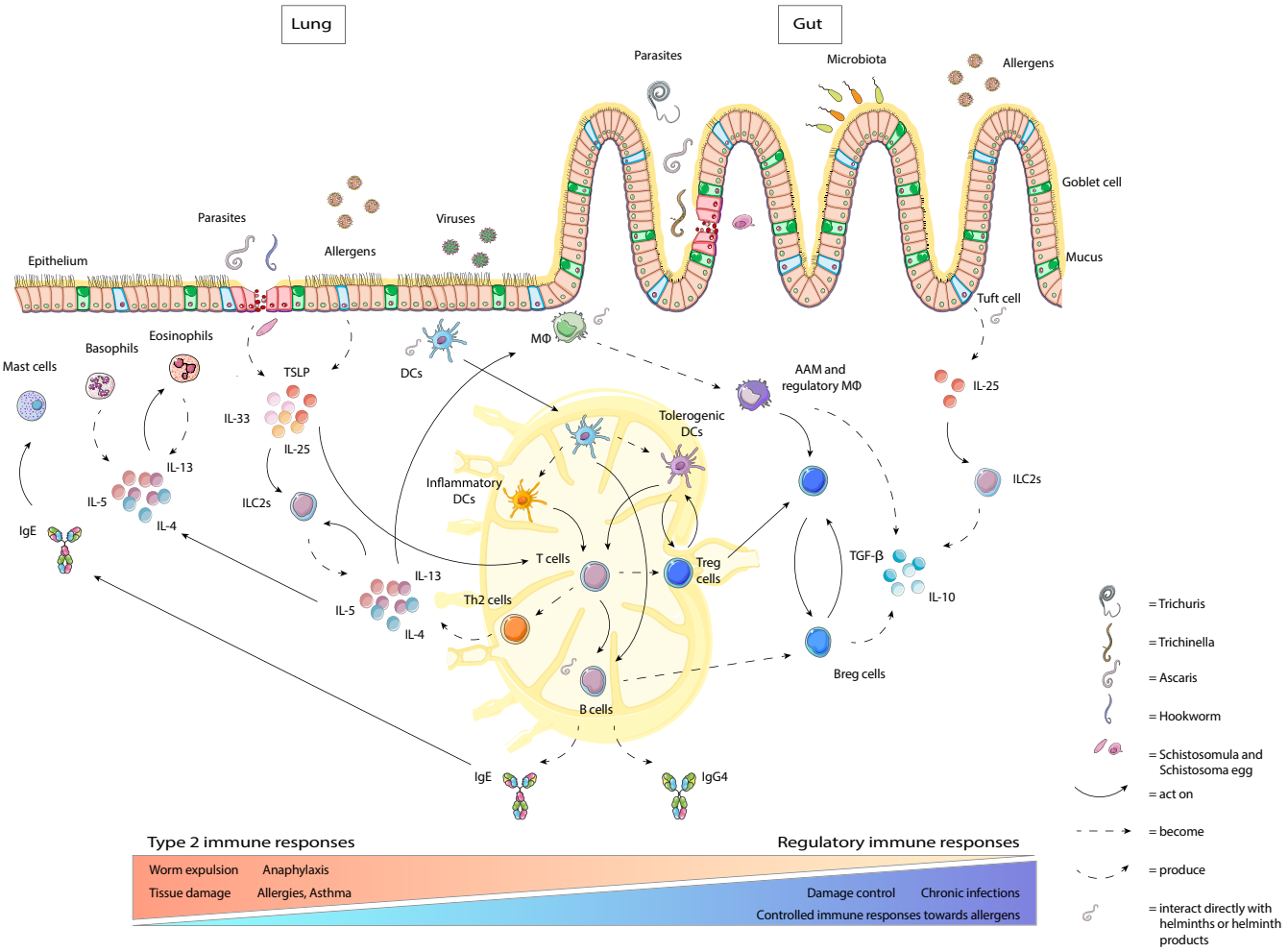


**FIGURE 2** Immune responses during helminth infections. Depending on their life cycle, various helminth species will pass or reside in (the proximity of) the lung and the gut. Consequently, damage will occur, leading to the release of alarmin cytokines IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) by epithelial cells and tuft cells (gut). These cytokines will act on innate lymphoid cells (ILC)2 and on dendritic cells (DCs), which will migrate to the draining lymph node and skew naïve T cells towards polarized Th2 cells, producing the cytokines IL-4, IL-5 and IL-13, in a similar fashion as ILC2s. These cytokines are central to the type 2 immune response and drive the isotype switch to IgE immunoglobulins, act on eosinophils, mast cells and drive the development of alternatively activated macrophages. All these elements are instrumental in worm expulsion but can also promote tissue damage, anaphylaxis and allergic responses towards bystander antigens. These responses are balanced by various cells from the regulatory network: for example regulatory T and B cells, regulatory macrophages and tolerogenic DCs. These regulatory cells can act on other cell types directly or through the production of anti-inflammatory cytokines IL-10 and TGF-β, as well as by the induction of anti-inflammatory IgG4, leading to immune tolerance and damage control, but at the same time prevent worm expulsion, promoting chronic helminth infections. Image is adapted from Servier Medical ART

In the following sections, we will focus on mechanisms by which type 2 immune responses are suppressed or induced in helminth infections, and how this could affect allergic responses (Figure 2 for a schematic overview). A deeper understanding of the interaction between helminths and their host will help to translate these mechanisms into a better therapeutic approach.

## 6 | HELMINTHS AND MODULATION OF ALLERGIC DISEASE: THE ROLE OF IMMUNOGLOBULINS, REGULATORY CELLS AND CYTOKINE INHIBITORS

### 6.1 | Immunoglobulins

Allergen-specific IgE is the defining characteristic of atopy, and in high-income countries, allergen-specific IgE strongly correlates with functional allergy measured by SPT reactivity. However, in helminth-endemic areas (especially rural areas of low socioeconomic status), this relationship often breaks down.[89,90] Furthermore, multiple epidemiological studies have shown a positive association between antihelminth IgE (ascariasis, schistosomiasis, filariasis) and wheeze and/or atopy.[91-95] One of the reasons for discrepancies between IgE reactivity (against allergen or helminth) and allergy in high-income versus helminth-endemic areas might be due to cross-reactivity of antihelminth IgE to certain allergens. For example, IgE against tropomyosin from *Onchocerca volvulus* cross-reacts with the tropomyosin of house dust mite Der p 10, boosting allergic responses to HDM.[96,97] While IgE against carbohydrates on Schistosoma egg glycoproteins can cross-react with cross-reactive carbohydrate determinants (CCDs) on peanut antigens, due to the low affinity of this IgE, cross-linking and degranulation of carbohydrate-specific IgE-coated mast cells do not occur. Therefore, these cross-reactive responses have the potential to block clinical responses to allergens like peanut.[98] Further studies are needed to clarify whether high levels of circulating cross-reactive protein or carbohydrate-specific IgE are instrumental in inducing or preventing allergic (skin) reactivity.[89]

The immunoglobulin isotype IgG4 is often associated with a tolerized allergic response following allergen-specific immunotherapy, and its production is also increased in many helminth-infected individuals.[99,100] Although there is a growing awareness of potentially harmful effects of IgG4 in several IgG4-related systemic diseases,[101] it is unclear how this pathogenic role of IgG4 compares to active tolerance induction to allergens or during helminth infection. Despite these recent reports on IgG4-related diseases, IgG4 antibodies are considered the least inflammatory of all isotypes—they do not activate complement, and unlike IgE they do not cause degranulation of mast cells. Due to the unique ability of IgG4 to swap antigen-binding arms, it is regarded as functionally monovalent and thus will not cause immune complex formation.[100] Thus, in this context, its main function appears to be a blocking one, and possibly instrumental in preventing IgE-mediated inflammation. High levels of anti-*Ascaris* IgG4 have been negatively associated with allergen SPT positivity,[102] while in a *S. mansoni*-endemic area—although higher levels of both IgE and IgG4 were found in infected individuals—a higher ratio of IgE to IgG4 predicted clinical allergic symptoms,[103] just as in allergen-specific immunotherapy.[104] As many helminth products are homologous to common allergens, IgG4 responses raised against helminth products may also bind and block IgE epitopes on allergens, reducing responses to allergens and directly reducing SPT responses.[105-107] Mechanistic research into the role of IgE and/or IgG4 is hampered by the lack of good experimental animal models, as IgG4 does not exist in mice.

### 6.2 | Regulatory cells

Both regulatory T cells (Tregs) and regulatory B cells (Bregs) are important in the control of type 2 immune responses and allergic airway inflammation in mouse models.[108] In individuals tolerized to allergens through high-dose environmental exposure or allergen-specific immunotherapy, levels of Tregs and Bregs are increased and required for maintenance of tolerance.[108] Both Tregs and Bregs can produce the immunosuppressive cytokines IL-10 and TGF-β, which can suppress damaging inflammation.[109]

IL-10 and TGF-β are also instrumental in immunosuppressive effects in a number of different helminths, including *Onchocerca*, *Ascaris*, *Trichuris* or *Toxocara* spp,[110-112] and appear to be important in suppression of allergic responses. Indeed, IL-10 was linked to a lower risk of allergic skin reactivity in schistosome-infected Gabonese schoolchildren.[113] Elevated numbers of circulating FOXP3+ CD25+ Treg cells have been demonstrated in *Schistosoma haematobium*[114] and filaria-infected people,[115] while anthelmintic treatment of *S. haematobium* or geohelminth-infected individuals leads to a normalization of circulating FOXP3 Treg or PD-1 and CTLA-4-expressing $CD4^+$ T cells[116] and/or subsequent increased in vitro cytokine responses to both helminth and bystander antigens.[114] Similarly, increased levels of Breg cells have been detected in helminth-infected MS patients[77] and in *S. haematobium*-infected Gabonese people.[45,117]

Also in mouse models of allergic airway inflammation (AAI), both helminth-induced Treg and Breg cells are instrumental in preventing disease symptoms. For example, Tregs from *H. polygyrus* or *T. spiralis*-infected mice transferred protection against airway pathology in models of experimental airway allergy.[43,46,118] *Heligmosomoides polygyrus* excretory/secretory products (HES) can induce Tregs in vitro, and transfer of HES-induced Tregs can replicate the suppressive capacity of the parasitic infection.[119] Recently, a TGF-β mimic (Hp-TGM) was identified in HES, a protein which alone can induce Tregs in vitro.[120,121]

Likewise, mesenteric lymph node $CD23^{hi}$ B cells from *H. polygyrus*-infected mice suppress allergic airway inflammation in an IL-10-independent manner,[122] while splenic marginal zone $CD1d^{hi}$ B cells from *S. mansoni*-infected mice induced protection in an IL-10 and Treg cell-dependent manner upon adoptive transfer.[45,123] Analysis of splenic $CD1d^{hi}$ B cells from schistosome-infected mice showed increased *Tlr7* expression, and TLR-7 ligation increased the IL-10 production in splenic $CD1d^{hi}$ B cells from naïve animals.[124]

Adoptive transfer of TLR-7 stimulated splenic CD1d$^{hi}$ B cells reduced allergic airway inflammation through the recruitment of regulatory T cells. Further mechanistic insight was recently supplied by the finding that the *S. mansoni*-derived molecule IPSE/alpha-1 could drive Breg differentiation in vitro.[125] In addition, and separately to "conventional" IL-10-producing Bregs, *S. mansoni*-infected mouse lungs also contain a nonclassical regulatory B-cell population that could also inhibit AAI by reducing allergen-specific Th2 responses, in an IL-10 and Treg-independent manner.[126]

These studies point towards an important role for helminth-induced Tregs and Bregs in the suppression of allergen-specific immune responses. However, part of these processes may also be accelerated by exhausted and hyporesponsive T- and B-cell responses.[127-130] For example, in murine *L. sigmodontis* infection, Th2 cells upregulate GITR, CTLA-4 and PD-1 and become hyporesponsive to stimuli,[131-134] while in chronic murine schistosome infection, hyporesponsive Th2 cells were linked to the anergy marker GRAIL.[135] Thus, in chronic Th2 dominated models, such as helminth infection, Th2 cells become hyporesponsive and anergic. This is to the benefit of both the parasite (allowing survival) and, often, the host (preventing inflammatory damage). Likewise, in allergen immunotherapy, through either anergy or deletion, Th2 cells decrease in number, reducing IL-4, IL-5 and IL-13 production.[136] Thus, hyporesponsive Th2 cells may share similar features in chronic helminth infection and tolerized allergic responses, however, whether this is an active process, and whether helminth infection causes hyporesponsiveness in bystander allergic responses in vivo is presently unclear.

### 6.3 | Myeloid cells

Dendritic cells (DC) are the critical link between innate and adaptive immunity and decide on the development of effector versus regulatory T-cell development based on their ontogeny, tissue location and/or environmental signals present. Different myeloid DC subsets—conventional type 1 (cDC1) and type 2 dendritic cells (cDC2)—can be distinguished on the basis of several surface expression markers recently identified in an unbiased approach across tissues and species[137,138]. While cDC1 can produce high levels of IL-12p70 and prime cytotoxic CD8 T-cell and antitumour responses, cDC2 can boost both Th17 or Th2 cells depending on the environment and show superior allergen uptake compared to cDC1.[139-144] Interestingly, cDC1 can also have a tolerogenic function in allergy models: they induce Treg cells via retinoic acid and peroxisome proliferator-activated receptor gamma (PPARγ) and limit inflammation in a HDM and ovalbumin model of allergic airway inflammation[145] and during schistosome infections.[146] In patients with asthma, increased numbers of DCs are found in the blood, induced sputum and bronchoalveolar lavage upon allergen challenge, but only cDC2 migrated into the bronchial tissue.[147] The DCs express more OX-40L, a molecule involved in Th2 polarization[148] and more FcεRI.[149] In the absence of DCs, type 2 responses in allergy models are profoundly abrogated,[150] but other myeloid cell populations may also be important to support Th2 cell development in either allergy models or helminth infection, like monocyte-derived dendritic cells.[140,141]

Macrophages differentiate into alternatively activated or M2 macrophages in response to IL-4 and IL-13. They can be distinguished from classically activated or M1 macrophages by the upregulation of markers such as RELM-α, Ym1 and arginase and are associated with wound healing and parasite killing.[11,151] M2 macrophages are also anti-inflammatory, producing IL-10 and TGFβ[152] and arginase, which restrict T-cell function through amino acid starvation[153] and suppress liver fibrosis in *S. mansoni* infection.[154] Furthermore, retinoid acid production by M2 macrophages during *S. mansoni* infections promotes the development of Treg cells at the sites of inflammation.[155] In allergic asthma, macrophages are considered to play a key role in inflammatory responses associated with lung injury, fibrosis and goblet cell hyperplasia[156] and stimulating smooth muscle cell contraction and extracellular cell matrix degradation, contributing to airway remodelling. Increased numbers of mannose receptor (MR)+ macrophages (a surface marker for M2 macrophages) are found in the bronchial tissue of allergic asthmatic patients.[157]

Immature or tolerogenic dendritic cells—induced by immunosuppressive drugs or molecules, like vitamin D3[158]—are potent drivers of regulatory T cells and immune tolerance. The ES products of *Ancylostoma caninum* can suppress immunopathology in mouse models of colitis.[159] Recently, AIP-1 (from the human hookworm *N. americanus*) and AIP-2 (from *A. caninum*) were shown to be suppressive in mouse models of colitis[160] and asthma[161] by a mechanism dependent on Treg expansion. Although the full mechanism of action of these molecules has yet to be elucidated, it appears that they achieve Treg expansion through modulation of dendritic cell responses.[161]

Likewise, regulatory macrophage populations can express IL-10 that is instrumental in Treg development and/or suppression of local immune responses. Both regulatory DC and macrophages are heavily exploited in immune evasive strategies by various pathogens.[162] This suppression also occurs in vivo, with changes in DC maturation status and phenotype and Treg-inducing function during experimental murine helminth infection,[163-165] with helminth product-induced macrophage IL-10 expression[166,167] and in human helminth-endemic populations.[168,169] In addition, adoptive transfer of tolerogenic DCs from *S. japonicum*-infected or *H. polygyrus*-infected mice reduced ovalbumin-induced AAI or colitis in uninfected recipients via IL-10.[165,170] Thus, both macrophages and DCs are capable of differentiating into inflammatory or suppressive phenotypes, both pathways being prone to helminth immunomodulation.

Both macrophages and DCs are modulated by parasite products through pattern recognition receptors (PRR), such as the TLR family and the C-type lectin receptors. Helminths secrete many molecules, a significant majority of which are decorated with glycans that play a role in parasite-host interactions.[171] The failure of live hookworm or TSO clinical trials has fuelled the interest in the immunomodulatory properties of helminth molecules and their glycans as potential therapeutic agents. Examples of immunomodulatory glycans or glycoproteins in the modulation of dendritic cell function and/or disease models are described for glycans from *Trichuris* eggs in TSO, the *S. mansoni* egg glycoprotein, omega-1—a T2 RNase—and the glycoprotein ES-62 secreted by *Acanthocheilonema viteae*.[172-175]

Other molecules that act on dendritic cell/macrophage function and dampen experimental allergic airway inflammation are identified from *Clonorchis sinensis*, *A. caninum*, *A. viteae*, *Brugia malayi* and *Anisakis simplex*.[161,166,167,176-178] Further studies are needed to clarify whether these molecules can also be used in allergic and asthmatic patients in a therapeutic setting without the disadvantages of the infection itself.

### 6.4 | Innate lymphoid and epithelial cells

The importance of early, innate, epithelial cell-derived cytokines in type 2 response initiation has only recently begun to be understood. The epithelial cell cytokines IL-25, IL-33 and TSLP activate ILC2s at barrier sites, which secrete large amounts of IL-5, IL-13 and IL-9. Recently, it was shown that ILC2s can also be activated to produce IL-10, providing a immunoregulatory pathway (similar to that seen in T cells) which could be amenable to parasite immunomodulation.[9]

Proximal epithelial cell responses therefore represent an ideal target for intervention, as blocking these cytokines could blunt downstream ILC, dendritic cell and T-cell responses. However, as these pathways have only recently been characterized, research into their suppression remains in its infancy. One exception is the IL-33 pathway in *H. polygyrus* infection, in which multiple parasite immunomodulatory factors have been identified. *Heligmosomoides polygyrus* excretory/secretory products (HES) replicate the suppressive effect of parasitic infection in suppression of airway allergic inflammation,[179] via abrogation of the earliest ILC2 responses to an allergen preparation from *Alternaria alternata*,[53] a clinically relevant stimulus. *Alternaria* allergen administration is a uniquely potent stimulus for IL-33 release,[180] and HES administration blocks the IL-33 pathway through induction of IL-1β (counter-regulating IL-25 and IL-33 expression),[181] miRNA-containing HES extracellular vesicles which reduce IL-33 receptor expression, and HpARI, a protein in HES which directly binds IL-33, abrogating its release.[54]

Recently, it was shown that cholinergic neurons activate[182-184] and adrenergic neurons inhibit[185] ILC2 responses, while type 2 cytokines in turn activate neurons,[186] forming a new field of neuroimmune interactions for future studies, and potential helminth modulation.

## 7 | CONCLUDING REMARKS

Helminth parasites have coevolved with their mammalian hosts for millions of years, and in doing so have developed an intimate relationship. On the one hand, this relationship can be seen as antagonistic, with the parasite attempting to subvert immune responses to its own ends, while the host immune system attempts to damage or kill the parasite. Alternatively, it can be seen as a mutualistic interaction, with parasite immunomodulation expected by the host immune system, and in fact required for healthy immune development, and avoidance of immune-mediated disease. It is likely that both forms of interaction occur, depending on context, parasite and environment. "Gene-environment" interactions in allergy and helminth infections are further complicated by "infection-environment" interactions with diet, living conditions depending on the socioeconomic status and/or rural versus urbanization sanitation, microbiota and coinfections, all of which have roles in the response to, and tolerance of, allergenic stimuli. By learning how, at the molecular level, these interactions occur; we may be able to replicate and tailor beneficial helminth-mediated effects for use in allergic disease, in the absence of the deleterious effects that come with parasitic infection.

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## REFERENCES

1. van de Veen W, Wirz OF, Globinska A, Akdis M. Novel mechanisms in immune tolerance to allergens during natural allergen exposure and allergen-specific immunotherapy. *Curr Opin Immunol*. 2017;48:74-81.
2. Nutman TB. Looking beyond the induction of Th2 responses to explain immunomodulation by helminths. *Parasite Immunol*. 2015;37:304-313.
3. Allen JE, Maizels RM. Diversity and dialogue in immunity to helminths. *Nat Rev Immunol*. 2011;11:375-388.
4. van Rijt LS, Jung S, Kleinjan A, et al. In vivo depletion of lung CD11c+ dendritic cells during allergen challenge abrogates the characteristic features of asthma. *J Exp Med*. 2005;201:981-991.
5. Phythian-Adams AT, Cook PC, Lundie RJ, et al. CD11c depletion severely disrupts Th2 induction and development in vivo. *J Exp Med*. 2010;207:2089-2096.
6. Hammad H, Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. *Immunity*. 2015;43:29-40.
7. Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev*. 2017;278:116-130.
8. Monticelli LA, Osborne LC, Noti M, Tran SV, Zaiss DM, Artis D. IL-33 promotes an innate immune pathway of intestinal tissue protection dependent on amphiregulin-EGFR interactions. *Proc Natl Acad Sci U S A*. 2015;112:10762-10767.
9. Seehus CR, Kadavallore A, Torre B, et al. Alternative activation generates IL-10 producing type 2 innate lymphoid cells. *Nat Commun*. 2017;8:1900.
10. Oliphant CJ, Hwang YY, Walker JA, et al. MHCII-mediated dialog between Group 2 innate lymphoid cells and $CD4^+$ T cells potentiates Type 2 immunity and promotes parasitic helminth expulsion. *Immunity*. 2014;41:283-295.
11. Harris NL, Loke P. Recent advances in type-2-cell-mediated immunity: insights from helminth infection. *Immunity*. 2017;47:1024-1036.
12. Maizels RM. Parasite immunomodulation and polymorphisms of the immune system. *J Biol*. 2009;8:62.
13. Costa RD, Figueiredo CA, Barreto ML, et al. Effect of polymorphisms on TGFB1 on allergic asthma and helminth infection in an African admixed population. *Ann Allergy Asthma Immunol*. 2017;118(483–488):e481.
14. Figueiredo CA, Barreto ML, Alcantara-Neves NM, et al. Coassociations between IL10 polymorphisms, IL-10 production,

helminth infection, and asthma/wheeze in an urban tropical population in Brazil. *J Allergy Clin Immunol*. 2013;131:1683-1690.
15. McSorley HJ, Maizels RM. Helminth infections and host immune regulation. *Clin Microbiol Rev*. 2012;25:585-608.
16. Mbow M, Larkin BM, Meurs L, et al. T-helper 17 cells are associated with pathology in human schistosomiasis. *J Infect Dis*. 2013;207:186-195.
17. Nogueira DS, Gazzinelli-Guimaraes PH, Barbosa FS, et al. Multiple exposures to *Ascaris suum* induce tissue injury and mixed Th2/Th17 immune response in mice. *PLoS Negl Trop Dis*. 2016;10:e0004382.
18. Babu S, Bhat SQ, Pavan Kumar N, et al. Filarial lymphedema is characterized by antigen-specific Th1 and th17 proinflammatory responses and a lack of regulatory T cells. *PLoS Negl Trop Dis*. 2009;3:e420.
19. Jia TW, Melville S, Utzinger J, King CH, Zhou XN. Soil-transmitted helminth reinfection after drug treatment: a systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2012;6:e1621.
20. Turner JE, Morrison PJ, Wilhelm C, et al. IL-9-mediated survival of type 2 innate lymphoid cells promotes damage control in helminth-induced lung inflammation. *J Exp Med*. 2013;210:2951-2965.
21. van Tong H, Brindley PJ, Meyer CG, Velavan TP. Parasite infection, carcinogenesis and human malignancy. *EBioMedicine*. 2017;15:12-23.
22. Duan Y, Pan J, Chen J, et al. Soluble egg antigens of *Schistosoma japonicum* induce senescence of activated hepatic stellate cells by activation of the FoxO3a/SKP2/P27 pathway. *PLoS Negl Trop Dis*. 2016;10:e0005268.
23. Smout MJ, Sotillo J, Laha T, et al. Carcinogenic parasite secretes growth factor that accelerates wound healing and potentially promotes neoplasia. *PLoS Pathog*. 2015;11:e1005209.
24. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet*. 2018;391:783-800.
25. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387:1109-1122.
26. Jones SM, Burks AW. Food allergy. *N Engl J Med*. 2017;377:1168-1176.
27. Tsai M, Starkl P, Marichal T, Galli SJ. Testing the 'toxin hypothesis of allergy': mast cells, IgE, and innate and acquired immune responses to venoms. *Curr Opin Immunol*. 2015;36:80-87.
28. Torow N, Marsland BJ, Hornef MW, Gollwitzer ES. Neonatal mucosal immunology. *Mucosal Immunol*. 2017;10:5-17.
29. Saluzzo S, Gorki AD, Rana BMJ, et al. First-breath-induced type 2 pathways shape the lung immune environment. *Cell Rep*. 2017;18:1893-1905.
30. Mallol J, Crane J, von Mutius E, et al. The International study of asthma and allergies in childhood (ISAAC) phase three: a global synthesis. *Allergol Immunopathol (Madr)*. 2013;41:73-85.
31. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. *Parasit Vectors*. 2014;7:37.
32. Potter PC, Davis G, Manjra A, Luyt D. House dust mite allergy in Southern Africa–historical perspective and current status. *Clin Exp Allergy*. 1996;26:132-137.
33. Leonardi-Bee J, Pritchard D, Britton J. Asthma and current intestinal parasite infection: systematic review and meta-analysis. *Am J Respir Crit Care Med*. 2006;174:514-523.
34. Feary J, Britton J, Leonardi-Bee J. Atopy and current intestinal parasite infection: a systematic review and meta-analysis. *Allergy*. 2011;66:569-578.
35. Wammes LJ, Mpairwe H, Elliott AM, Yazdanbakhsh M. Helminth therapy or elimination: epidemiological, immunological, and clinical considerations. *Lancet Infect Dis*. 2014;14:1150-1162.
36. Santiago HC, Nutman TB. Human helminths and allergic disease: the hygiene hypothesis and beyond. *Am J Trop Med Hyg*. 2016;95:746-753.
37. Endara P, Vaca M, Chico ME, et al. Long-term periodic anthelmintic treatments are associated with increased allergen skin reactivity. *Clin Exp Allergy*. 2010;40:1669-1677.
38. Cooper PJ, Chico ME, Vaca MG, et al. Effect of albendazole treatments on the prevalence of atopy in children living in communities endemic for geohelminth parasites: a cluster-randomised trial. *Lancet*. 2006;367:1598-1603.
39. Cooper PJ. Interactions between helminth parasites and allergy. *Curr Opin Allergy Clin Immunol*. 2009;9:29-37.
40. Mpairwe H, Tweyongyere R, Elliott A. Pregnancy and helminth infections. *Parasite Immunol*. 2014;36:328-337.
41. Namara B, Nash S, Lule SA, et al. Effects of treating helminths during pregnancy and early childhood on risk of allergy-related outcomes: follow-up of a randomized controlled trial. *Pediatr Allergy Immunol*. 2017;28:784-792.
42. Wohlleben G, Trujillo C, Muller J, et al. Helminth infection modulates the development of allergen-induced airway inflammation. *Int Immunol*. 2004;16:585-596.
43. Wilson MS, Taylor MD, Balic A, Finney CA, Lamb JR, Maizels RM. Suppression of allergic airway inflammation by helminth-induced regulatory T cells. *J Exp Med*. 2005;202:1199-1212.
44. Dittrich AM, Erbacher A, Specht S, et al. Helminth infection with *Litomosoides sigmodontis* induces regulatory T cells and inhibits allergic sensitization, airway inflammation, and hyperreactivity in a murine asthma model. *J Immunol*. 2008;180:1792-1799.
45. van der Vlugt LE, Labuda LA, Ozir-Fazalalikhan A, et al. Schistosomes induce regulatory features in human and mouse CD1d(hi) B cells: inhibition of allergic inflammation by IL-10 and regulatory T cells. *PLoS ONE*. 2012;7:e30883.
46. Aranzamendi C, de Bruin A, Kuiper R, et al. Protection against allergic airway inflammation during the chronic and acute phases of *Trichinella spiralis* infection. *Clin Exp Allergy*. 2013;43:103-115.
47. Liu P, Li J, Yang X, et al. Helminth infection inhibits airway allergic reaction and dendritic cells are involved in the modulation process. *Parasite Immunol*. 2010;32:57-66.
48. Qiu S, Fan X, Yang Y, et al. *Schistosoma japonicum* infection downregulates house dust mite-induced allergic airway inflammation in mice. *PLoS ONE*. 2017;12:e0179565.
49. Straubinger K, Paul S, Prazeres da Costa O, et al. Maternal immune response to helminth infection during pregnancy determines offspring susceptibility to allergic airway inflammation. *J Allergy Clin Immunol*. 2014;134(1271–1279):e1210.
50. Burbank AJ, Sood AK, Kesic MJ, Peden DB, Hernandez ML. Environmental determinants of allergy and asthma in early life. *J Allergy Clin Immunol*. 2017;140:1-12.
51. Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet*. 2010;376:826-834.
52. Jackson DJ, Makrinioti H, Rana BM, et al. IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. *Am J Respir Crit Care Med*. 2014;190:1373-1382.
53. McSorley HJ, Blair NF, Smith KA, McKenzie AN, Maizels RM. Blockade of IL-33 release and suppression of type 2 innate lymphoid cell responses by helminth secreted products in airway allergy. *Mucosal Immunol*. 2014;7:1068-1078.
54. Osbourn M, Soares DC, Vacca F, et al. HpARI protein secreted by a helminth parasite suppresses interleukin-33. *Immunity*. 2017;47(739–751):e735.
55. Lynch JP, Werder RB, Simpson J, et al. Aeroallergen-induced IL-33 predisposes to respiratory virus-induced asthma by dampening antiviral immunity. *J Allergy Clin Immunol*. 2016;138:1326-1337.
56. McFarlane AJ, McSorley HJ, Davidson DJ, et al. Enteric helminth-induced type I interferon signaling protects against pulmonary

virus infection through interaction with the microbiota. *J Allergy Clin Immunol*. 2017;140(1068–1078):e1066.
57. Scheer S, Krempl C, Kallfass C, et al. S. mansoni bolsters anti-viral immunity in the murine respiratory tract. *PLoS ONE*. 2014;9:e112469.
58. Reese TA, Wakeman BS, Choi HS, et al. Helminth infection reactivates latent gamma-herpesvirus via cytokine competition at a viral promoter. *Science*. 2014;345:573-577.
59. Osborne LC, Monticelli LA, Nice TJ, et al. Coinfection. Virus-helminth coinfection reveals a microbiota-independent mechanism of immunomodulation. *Science*. 2014;345:578-582.
60. Reynolds LA, Finlay BB. Early life factors that affect allergy development. *Nat Rev Immunol*. 2017;17:518-528.
61. Huffnagle GB, Dickson RP, Lukacs NW. The respiratory tract microbiome and lung inflammation: a two-way street. *Mucosal Immunol*. 2017;10:299-306.
62. Lee SC, Tang MS, Lim YA, et al. Helminth colonization is associated with increased diversity of the gut microbiota. *PLoS Negl Trop Dis*. 2014;8:e2880.
63. Ramanan D, Bowcutt R, Lee SC, et al. Helminth infection promotes colonization resistance via type 2 immunity. *Science*. 2016;352:608-612.
64. Giacomin P, Zakrzewski M, Croese J, et al. Experimental hookworm infection and escalating gluten challenges are associated with increased microbial richness in celiac subjects. *Sci Rep*. 2015;5:13797.
65. Giacomin P, Zakrzewski M, Jenkins TP, et al. Changes in duodenal tissue-associated microbiota following hookworm infection and consecutive gluten challenges in humans with coeliac disease. *Sci Rep*. 2016;6:36797.
66. Fricke WF, Song Y, Wang AJ, et al. Type 2 immunity-dependent reduction of segmented filamentous bacteria in mice infected with the helminthic parasite *Nippostrongylus brasiliensis*. *Microbiome*. 2015;3:40.
67. Houlden A, Hayes KS, Bancroft AJ, et al. Chronic *Trichuris muris* infection in C57BL/6 mice causes significant changes in host microbiota and metabolome: effects reversed by pathogen clearance. *PLoS ONE*. 2015;10:e0125945.
68. Reynolds LA, Smith KA, Filbey KJ, et al. Commensal-pathogen interactions in the intestinal tract: lactobacilli promote infection with, and are promoted by, helminth parasites. *Gut Microbes*. 2014;5:522-532.
69. Cotton S, Donnelly S, Robinson MW, Dalton JP, Thivierge K. Defense peptides secreted by helminth pathogens: antimicrobial and/or immunomodulator molecules? *Front Immunol*. 2012;3:269.
70. Su C, Su L, Li Y, et al. Helminth-induced alterations of the gut microbiota exacerbate bacterial colitis. *Mucosal Immunol*. 2018;11:144-157.
71. Trompette A, Gollwitzer ES, Yadava K, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med*. 2014;20:159-166.
72. Zaiss MM, Rapin A, Lebon L, et al. The intestinal microbiota contributes to the ability of helminths to modulate allergic inflammation. *Immunity*. 2015;43:998-1010.
73. Summers RW, Elliott DE, Qadir K, Urban JF Jr, Thompson R, Weinstock JV. *Trichuris suis* seems to be safe and possibly effective in the treatment of inflammatory bowel disease. *Am J Gastroenterol*. 2003;98:2034-2041.
74. Summers RW, Elliott DE, Urban JF Jr, Thompson R, Weinstock JV. *Trichuris suis* therapy in Crohn's disease. *Gut*. 2005;54:87-90.
75. Summers RW, Elliott DE, Urban JF Jr, Thompson RA, Weinstock JV. *Trichuris suis* therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology*. 2005;128:825-832.
76. Correale J, Farez M. Association between parasite infection and immune responses in multiple sclerosis. *Ann Neurol*. 2007;61:97-108.
77. Correale J, Farez M, Razzitte G. Helminth infections associated with multiple sclerosis induce regulatory B cells. *Ann Neurol*. 2008;64:187-199.
78. Correale J, Farez MF. The impact of parasite infections on the course of multiple sclerosis. *J Neuroimmunol*. 2011;233:6-11.
79. Daveson AJ, Jones DM, Gaze S, et al. Effect of hookworm infection on wheat challenge in celiac disease–a randomised double-blinded placebo controlled trial. *PLoS ONE*. 2011;6:e17366.
80. McSorley HJ, Gaze S, Daveson J, et al. Suppression of inflammatory immune responses in celiac disease by experimental hookworm infection. *PLoS ONE*. 2011;6:e24092.
81. Gaze S, McSorley HJ, Daveson J, et al. Characterising the mucosal and systemic immune responses to experimental human hookworm infection. *PLoS Pathog*. 2012;8:e1002520.
82. Croese J, Giacomin P, Navarro S, et al. Experimental hookworm infection and gluten microchallenge promote tolerance in celiac disease. *J Allergy Clin Immunol*. 2015;135:508-516.
83. Scholmerich J, Fellermann K, Seibold FW, et al. A randomised, double-blind, placebo-controlled trial of *Trichuris suis* ova in active Crohn's disease. *J Crohns Colitis*. 2017;11:390-399.
84. Voldsgaard A, Bager P, Garde E, et al. *Trichuris suis* ova therapy in relapsing multiple sclerosis is safe but without signals of beneficial effect. *Mult Scler*. 2015;21:1723-1729.
85. Fleming J, Hernandez G, Hartman L, et al. Safety and efficacy of helminth treatment in relapsing-remitting multiple sclerosis: results of the HINT 2 clinical trial. *Mult Scler*. 2017; doi: 10.1177/1352458517736377 .
86. Feary JR, Venn AJ, Mortimer K, et al. Experimental hookworm infection: a randomized placebo-controlled trial in asthma. *Clin Exp Allergy*. 2010;40:299-306.
87. Blount D, Hooi D, Feary J, et al. Immunologic profiles of persons recruited for a randomized, placebo-controlled clinical trial of hookworm infection. *Am J Trop Med Hyg*. 2009;81:911-916.
88. Elliott DE, Weinstock JV. Nematodes and human therapeutic trials for inflammatory disease. *Parasite Immunol*. 2017;39:e12407.
89. Amoah AS, Boakye DA, Yazdanbakhsh M, van Ree R. Influence of parasitic worm infections on allergy diagnosis in sub-Saharan Africa. *Curr Allergy Asthma Rep*. 2017;17:65.
90. Obeng BB, Amoah AS, Larbi IA, et al. Schistosome infection is negatively associated with mite atopy, but not wheeze and asthma in Ghanaian schoolchildren. *Clin Exp Allergy*. 2014;44:965-975.
91. Alcantara-Neves NM, Badaro SJ, dos Santos MC, Pontes-de-Carvalho L, Barreto ML. The presence of serum anti-*Ascaris lumbricoides* IgE antibodies and of *Trichuris trichiura* infection are risk factors for wheezing and/or atopy in preschool-aged Brazilian children. *Respir Res*. 2010;11:114.
92. Moncayo AL, Vaca M, Oviedo G, et al. Effects of geohelminth infection and age on the associations between allergen-specific IgE, skin test reactivity and wheeze: a case-control study. *Clin Exp Allergy*. 2013;43:60-72.
93. Takeuchi H, Khan AF, Yunus M, et al. Anti-*Ascaris* immunoglobulin E associated with bronchial hyper-reactivity in 9-year-old rural Bangladeshi children. *Allergol Int*. 2016;65:141-146.
94. Ahumada V, Garcia E, Dennis R, et al. IgE responses to Ascaris and mite tropomyosins are risk factors for asthma. *Clin Exp Allergy*. 2015;45:1189-1200.
95. Webb EL, Nampijja M, Kaweesa J, et al. Helminths are positively associated with atopy and wheeze in Ugandan fishing communities: results from a cross-sectional survey. *Allergy*. 2016;71:1156-1169.
96. Acevedo N, Sanchez J, Erler A, et al. IgE cross-reactivity between Ascaris and domestic mite allergens: the role of tropomyosin and the nematode polyprotein ABA-1. *Allergy*. 2009;64:1635-1643.

97. Hamid F, Amoah AS, van Ree R, Yazdanbakhsh M. Helminth-induced IgE and protection against allergic disorders. *Curr Top Microbiol Immunol*. 2015;388:91-108.
98. Amoah AS, Obeng BB, Larbi IA, et al. Peanut-specific IgE antibodies in asymptomatic Ghanaian children possibly caused by carbohydrate determinant cross-reactivity. *J Allergy Clin Immunol*. 2013;132:639-647.
99. Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. *Clin Exp Allergy*. 2009;39:469-477.
100. Aalberse RC, Schuurman J. IgG4 breaking the rules. *Immunology*. 2002;105:9-19.
101. Bledsoe JR, Della-Torre E, Rovati L, Deshpande V. IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach. *APMIS*. 2018;126:459-476.
102. Cooper PJ, Chico ME, Rodrigues LC, et al. Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. *J Allergy Clin Immunol*. 2003;111:995-1000.
103. Nkurunungi G, Kabagenyi J, Nampijja M, et al. *Schistosoma mansoni*-specific immune responses and allergy in Uganda. *Parasite Immunol*. 2018;40:e12506.
104. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy*. 2017;72:1156-1173.
105. Doenhoff MJ, El-Faham M, Liddell S, et al. Cross-reactivity between schistosoma mansoni antigens and the latex allergen Hev b 7: putative implication of cross-reactive carbohydrate determinants (CCDs). *PLoS ONE*. 2016;11:e0159542.
106. Igetei JE, El-Faham M, Liddell S, Doenhoff MJ. Antigenic cross-reactivity between Schistosoma mansoni and peanut: a role for cross-reactive carbohydrate determinants (CCDs) and implications for the hygiene hypothesis. *Immunology*. 2017;150:506-517.
107. Igetei JE, El-Faham M, Liddell S, Schramm G, Doenhoff MJ. Antigenic cross-reactivity between Schistosoma mansoni and pollen allergens from the birch tree (Betula verrucosa) and Timothy grass (Phleum pratense): involvement of shared glycan epitopes and implications for the hygiene hypothesis. *Int J Parasitol*. 2018;48:345-357.
108. Palomares O, Akdis M, Martin-Fontecha M, Akdis CA. Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. *Immunol Rev*. 2017;278:219-236.
109. Hussaarts L, van der Vlugt LE, Yazdanbakhsh M, Smits HH. Regulatory B-cell induction by helminths: implications for allergic disease. *J Allergy Clin Immunol*. 2011;128:733-739.
110. Alcantara-Neves NM, de Britto SG, Veiga RV, et al. Effects of helminth co-infections on atopy, asthma and cytokine production in children living in a poor urban area in Latin America. *BMC Res Notes*. 2014;7:817.
111. Doetze A, Satoguina J, Burchard G, et al. Antigen-specific cellular hyporesponsiveness in a chronic human helminth infection is mediated by T(h)3/T(r)1-type cytokines IL-10 and transforming growth factor-beta but not by a T(h)1 to T(h)2 shift. *Int Immunol*. 2000;12:623-630.
112. Satoguina J, Mempel M, Larbi J, et al. Antigen-specific T regulatory-1 cells are associated with immunosuppression in a chronic helminth infection (onchocerciasis). *Microbes Infect*. 2002;4:1291-1300.
113. van den Biggelaar AH, van Ree R, Rodrigues LC, et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet*. 2000;356:1723-1727.
114. Schmiedel Y, Mombo-Ngoma G, Labuda LA, et al. CD4+CD25hiFOXP3+ regulatory T cells and cytokine responses in human schistosomiasis before and after treatment with praziquantel. *PLoS Negl Trop Dis*. 2015;9:e0003995.
115. Wammes LJ, Hamid F, Wiria AE, et al. Regulatory T cells in human lymphatic filariasis: stronger functional activity in microfilaremics. *PLoS Negl Trop Dis*. 2012;6:e1655.
116. Wammes LJ, Hamid F, Wiria AE, et al. Community deworming alleviates geohelminth-induced immune hyporesponsiveness. *Proc Natl Acad Sci U S A*. 2016;113:12526-12531.
117. van der Vlugt LE, Zinsou JF, Ozir-Fazalalikhan A, et al. Interleukin 10 (IL-10)-producing CD1dhi regulatory B cells from *Schistosoma haematobium*-infected individuals induce IL-10-positive T cells and suppress effector T-cell cytokines. *J Infect Dis*. 2014;210:1207-1216.
118. Kang SA, Park MK, Cho MK, et al. Parasitic nematode-induced CD4+Foxp3+T cells can ameliorate allergic airway inflammation. *PLoS Negl Trop Dis*. 2014;8:e3410.
119. Grainger JR, Smith KA, Hewitson JP, et al. Helminth secretions induce de novo T cell Foxp3 expression and regulatory function through the TGF-beta pathway. *J Exp Med*. 2010;207:2331-2341.
120. Johnston CJC, Smyth DJ, Kodali RB, et al. A structurally distinct TGF-beta mimic from an intestinal helminth parasite potently induces regulatory T cells. *Nat Commun*. 2017;8:1741.
121. Smyth DJ, Harcus Y, White MPJ, et al. TGF-beta mimic proteins form an extended gene family in the murine parasite *Heligmosomoides polygyrus*. *Int J Parasitol*. 2018;48:379-385.
122. Wilson MS, Taylor MD, O'Gorman MT, et al. Helminth-induced CD19+CD23hi B cells modulate experimental allergic and autoimmune inflammation. *Eur J Immunol*. 2010;40:1682-1696.
123. Amu S, Saunders SP, Kronenberg M, Mangan NE, Atzberger A, Fallon PG. Regulatory B cells prevent and reverse allergic airway inflammation via FoxP3-positive T regulatory cells in a murine model. *J Allergy Clin Immunol*. 2010;125(1114–1124):e1118.
124. Khan AR, Amu S, Saunders SP, et al. Ligation of TLR7 on CD19(+) CD1d(hi) B cells suppresses allergic lung inflammation via regulatory T cells. *Eur J Immunol*. 2015;45:1842-1854.
125. Haeberlein S, Obieglo K, Ozir-Fazalalikhan A, et al. Schistosome egg antigens, including the glycoprotein IPSE/alpha-1, trigger the development of regulatory B cells. *PLoS Pathog*. 2017;13:e1006539.
126. van der Vlugt L, Obieglo K, Ozir-Fazalalikhan A, Sparwasser T, Haeberlein S, Smits HH. Schistosome-induced pulmonary B cells inhibit allergic airway inflammation and display a reduced Th2-driving function. *Int J Parasitol*. 2017;47:545-554.
127. Babu S, Blauvelt CP, Kumaraswami V, Nutman TB. Regulatory networks induced by live parasites impair both Th1 and Th2 pathways in patent lymphatic filariasis: implications for parasite persistence. *J Immunol*. 2006;176:3248-3256.
128. Grogan JL, Kremsner PG, Deelder AM, Yazdanbakhsh M. Antigen-specific proliferation and interferon-gamma and interleukin-5 production are down-regulated during *Schistosoma haematobium* infection. *J Infect Dis*. 1998;177:1433-1437.
129. Sartono E, Kruize YC, Kurniawan A, Maizels RM, Yazdanbakhsh M. Depression of antigen-specific interleukin-5 and interferon-gamma responses in human lymphatic filariasis as a function of clinical status and age. *J Infect Dis*. 1997;175:1276-1280.
130. Labuda LA, Ateba-Ngoa U, Feugap EN, et al. Alterations in peripheral blood B cell subsets and dynamics of B cell responses during human schistosomiasis. *PLoS Negl Trop Dis*. 2013;7:e2094.
131. Taylor MD, LeGoff L, Harris A, Malone E, Allen JE, Maizels RM. Removal of regulatory T cell activity reverses hyporesponsiveness and leads to filarial parasite clearance in vivo. *J Immunol*. 2005;174:4924-4933.
132. Taylor MD, van der Werf N, Harris A, et al. Early recruitment of natural CD4+ Foxp3+ Treg cells by infective larvae determines the outcome of filarial infection. *Eur J Immunol*. 2009;39:192-206.
133. van der Werf N, Redpath SA, Phythian-Adams AT, et al. Th2 responses to helminth parasites can be therapeutically enhanced by,

but are not dependent upon, GITR-GITR ligand costimulation in vivo. *J Immunol*. 2011;187:1411-1420.
134. van der Werf N, Redpath SA, Azuma M, Yagita H, Taylor MD. Th2 cell-intrinsic hypo-responsiveness determines susceptibility to helminth infection. *PLoS Pathog*. 2013;9:e1003215.
135. Taylor JJ, Krawczyk CM, Mohrs M, Pearce EJ. Th2 cell hyporesponsiveness during chronic murine schistosomiasis is cell intrinsic and linked to GRAIL expression. *J Clin Invest*. 2009;119:1019-1028.
136. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol*. 2017;140:1485-1498.
137. Guilliams M, Dutertre CA, Scott CL, et al. Unsupervised high-dimensional analysis aligns dendritic cells across tissues and species. *Immunity*. 2016;45:669-684.
138. Alcantara-Hernandez M, Leylek R, Wagar LE, et al. High-dimensional phenotypic mapping of human dendritic cells reveals interindividual variation and tissue specialization. *Immunity*. 2017;47(1037–1050):e1036.
139. Geginat J, Nizzoli G, Paroni M, et al. Immunity to pathogens taught by specialized human dendritic cell subsets. *Front Immunol*. 2015;6:527.
140. Plantinga M, Guilliams M, Vanheerswynghels M, et al. Conventional and monocyte-derived CD11b(+) dendritic cells initiate and maintain T helper 2 cell-mediated immunity to house dust mite allergen. *Immunity*. 2013;38:322-335.
141. Gao Y, Nish SA, Jiang R, et al. Control of T helper 2 responses by transcription factor IRF4-dependent dendritic cells. *Immunity*. 2013;39:722-732.
142. Williams JW, Tjota MY, Clay BS, et al. Transcription factor IRF4 drives dendritic cells to promote Th2 differentiation. *Nat Commun*. 2013;4:2990.
143. Tussiwand R, Everts B, Grajales-Reyes GE, et al. Klf4 expression in conventional dendritic cells is required for T helper 2 cell responses. *Immunity*. 2015;42:916-928.
144. de Kouchkovsky DA, Ghosh S, Rothlin CV. Negative regulation of type 2 immunity. *Trends Immunol*. 2017;38:154-167.
145. Bernatchez E, Gold MJ, Langlois A, et al. Pulmonary CD103 expression regulates airway inflammation in asthma. *Am J Physiol Lung Cell Mol Physiol*. 2015;308:L816-L826.
146. Everts B, Tussiwand R, Dreesen L, et al. Migratory CD103+ dendritic cells suppress helminth-driven type 2 immunity through constitutive expression of IL-12. *J Exp Med*. 2016;213:35-51.
147. El-Gammal A, Oliveria JP, Howie K, et al. Allergen-induced changes in bone marrow and airway dendritic cells in subjects with asthma. *Am J Respir Crit Care Med*. 2016;194:169-177.
148. Bleck B, Kazeros A, Bakal K, et al. Coexpression of type 2 immune targets in sputum-derived epithelial and dendritic cells from asthmatic subjects. *J Allergy Clin Immunol*. 2015;136(619–627):e615.
149. Greer AM, Matthay MA, Kukreja J, et al. Accumulation of BDCA1(+) dendritic cells in interstitial fibrotic lung diseases and Th2-high asthma. *PLoS ONE*. 2014;9:e99084.
150. Hammad H, Plantinga M, Deswarte K, et al. Inflammatory dendritic cells–not basophils–are necessary and sufficient for induction of Th2 immunity to inhaled house dust mite allergen. *J Exp Med*. 2010;207:2097-2111.
151. Ruckerl D, Allen JE. Macrophage proliferation, provenance, and plasticity in macroparasite infection. *Immunol Rev*. 2014;262:113-133.
152. Shapouri-Moghaddam A, Mohammadian S, Vazini H, et al. Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol*. 2018;233:6425-6440.
153. Van de Velde LA, Subramanian C, Smith AM, et al. T cells encountering myeloid cells programmed for amino acid-dependent immunosuppression use rictor/mTORC2 protein for proliferative checkpoint decisions. *J Biol Chem*. 2017;292:15-30.
154. Pesce JT, Ramalingam TR, Mentink-Kane MM, et al. Arginase-1-expressing macrophages suppress Th2 cytokine-driven inflammation and fibrosis. *PLoS Pathog*. 2009;5:e1000371.
155. Broadhurst MJ, Leung JM, Lim KC, et al. Upregulation of retinal dehydrogenase 2 in alternatively activated macrophages during retinoid-dependent type-2 immunity to helminth infection in mice. *PLoS Pathog*. 2012;8:e1002883.
156. Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. *Nature*. 2013;496:445-455.
157. Draijer C, Boorsma CE, Robbe P, et al. Human asthma is characterized by more IRF5+ M1 and CD206+ M2 macrophages and less IL-10+ M2-like macrophages around airways compared with healthy airways. *J Allergy Clin Immunol*. 2017;140(280–283):e283.
158. Sato K, Uto T, Fukaya T, Takagi H. Regulatory dendritic cells. *Curr Top Microbiol Immunol*. 2017;410:47-71.
159. Ferreira I, Smyth D, Gaze S, et al. Hookworm excretory/secretory products induce interleukin-4 (IL-4)+ IL-10+ CD4+ T cell responses and suppress pathology in a mouse model of colitis. *Infect Immun*. 2013;81:2104-2111.
160. Ferreira IB, Pickering DA, Troy S, Croese J, Loukas A, Navarro S. Suppression of inflammation and tissue damage by a hookworm recombinant protein in experimental colitis. *Clin Transl Immunology*. 2017;6:e157.
161. Navarro S, Pickering DA, Ferreira IB, et al. Hookworm recombinant protein promotes regulatory T cell responses that suppress experimental asthma. *Sci Transl Med*. 2016;8:362ra143.
162. Rescigno M. Dendritic cell functions: Learning from microbial evasion strategies. *Semin Immunol*. 2015;27:119-124.
163. Sharma A, Sharma P, Vishwakarma AL, Srivastava M. Functional impairment of murine dendritic cell subsets following infection with infective larval stage 3 of *Brugia malayi*. *Infect Immun*. 2017;85:e00818-16.
164. Smith KA, Hochweller K, Hammerling GJ, Boon L, MacDonald AS, Maizels RM. Chronic helminth infection promotes immune regulation in vivo through dominance of CD11cloCD103- dendritic cells. *J Immunol*. 2011;186:7098-7109.
165. Blum AM, Hang L, Setiawan T, et al. *Heligmosomoides polygyrus bakeri* induces tolerogenic dendritic cells that block colitis and prevent antigen-specific gut T cell responses. *J Immunol*. 2012;189:2512-2520.
166. Schnoeller C, Rausch S, Pillai S, et al. A helminth immunomodulator reduces allergic and inflammatory responses by induction of IL-10-producing macrophages. *J Immunol*. 2008;180:4265-4272.
167. Ziegler T, Rausch S, Steinfelder S, et al. A novel regulatory macrophage induced by a helminth molecule instructs IL-10 in CD4+ T cells and protects against mucosal inflammation. *J Immunol*. 2015;194:1555-1564.
168. Everts B, Adegnika AA, Kruize YC, Smits HH, Kremsner PG, Yazdanbakhsh M. Functional impairment of human myeloid dendritic cells during *Schistosoma haematobium* infection. *PLoS Negl Trop Dis*. 2010;4:e667.
169. Nausch N, Louis D, Lantz O, et al. Age-related patterns in human myeloid dendritic cell populations in people exposed to *Schistosoma haematobium* infection. *PLoS Negl Trop Dis*. 2012;6:e1824.
170. Liu JY, Lu P, Hu LZ, et al. CD8alpha DC is the major DC subset which mediates inhibition of allergic responses by *Schistosoma* infection. *Parasite Immunol*. 2014;36:647-657.
171. Hokke CH, van Diepen A. Helminth glycomics – glycan repertoires and host-parasite interactions. *Mol Biochem Parasitol*. 2017;215:47-57.
172. Everts B, Hussaarts L, Driessen NN, et al. Schistosome-derived omega-1 drives Th2 polarization by suppressing protein synthesis following internalization by the mannose receptor. *J Exp Med*. 2012;209(1753–1767):S1751.

173. Everts B, Perona-Wright G, Smits HH, et al. Omega-1, a glycoprotein secreted by *Schistosoma mansoni* eggs, drives Th2 responses. *J Exp Med*. 2009;206:1673-1680.
174. Zaccone P, Burton OT, Gibbs SE, et al. The *S. mansoni* glycoprotein omega-1 induces Foxp3 expression in NOD mouse CD4(+) T cells. *Eur J Immunol*. 2011;41:2709-2718.
175. Suckling CJ, Alam S, Olson MA, Saikh KU, Harnett MM, Harnett W. Small molecule analogues of the parasitic worm product ES-62 interact with the TIR domain of MyD88 to inhibit pro-inflammatory signalling. *Sci Rep*. 2018;8:2123.
176. Liu JY, Li LY, Yang XZ, et al. Adoptive transfer of dendritic cells isolated from helminth-infected mice enhanced T regulatory cell responses in airway allergic inflammation. *Parasite Immunol*. 2011;33:525-534.
177. Pastrana DV, Raghavan N, FitzGerald P, et al. Filarial nematode parasites secrete a homologue of the human cytokine macrophage migration inhibitory factor. *Infect Immun*. 1998;66:5955-5963.
178. Park SK, Cho MK, Park HK, et al. Macrophage migration inhibitory factor homologs of *Anisakis simplex* suppress Th2 response in allergic airway inflammation model via CD4+CD25+Foxp3+ T cell recruitment. *J Immunol*. 2009;182:6907-6914.
179. McSorley HJ, O'Gorman MT, Blair N, Sutherland TE, Filbey KJ, Maizels RM. Suppression of type 2 immunity and allergic airway inflammation by secreted products of the helminth *Heligmosomoides polygyrus*. *Eur J Immunol*. 2012;42:2667-2682.
180. Kouzaki H, Iijima K, Kobayashi T, O'Grady SM, Kita H. The danger signal, extracellular ATP, is a sensor for an airborne allergen and triggers IL-33 release and innate Th2-type responses. *J Immunol*. 2011;186:4375-4387.
181. Zaiss MM, Maslowski KM, Mosconi I, Guenat N, Marsland BJ, Harris NL. IL-1beta suppresses innate IL-25 and IL-33 production and maintains helminth chronicity. *PLoS Pathog*. 2013;9:e1003531.
182. Cardoso V, Chesne J, Ribeiro H, et al. Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. *Nature*. 2017;549:277-281.
183. Klose CSN, Mahlakoiv T, Moeller JB, et al. The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature*. 2017;549:282-286.
184. Wallrapp A, Riesenfeld SJ, Burkett PR, et al. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature*. 2017;549:351-356.
185. Moriyama S, Brestoff JR, Flamar AL, et al. Beta2-adrenergic receptor-mediated negative regulation of group 2 innate lymphoid cell responses. *Science*. 2018;359:1056-1061.
186. Foster SL, Seehus CR, Woolf CJ, Talbot S. Sense and immunity: context-dependent neuro-immune interplay. *Front Immunol*. 2017;8:1463.

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